

Amendments to the Specification:

Please replace the existing cross-reference to related applications section with the following replacement section.

This application is a continuation of U.S. Application No. 09/585,817, filed June 1, 2000, which claims the benefit under 35 U.S.C. 119(e) of U.S. Application No. 60/137,010, filed June 1, 1999, which is hereby incorporated herein in its entirety. This application is also a continuation of U.S. Application No. 09/585,817, filed June 1, 2000, which is a continuation-in-part of U.S. Application No. 09/580,015, filed May 26, 2000, which is a continuation-in-part of U.S. Application No. 09/322,289, filed May 28, 1999, which is a continuation in part of U.S. 09/201,430, filed November 30, 1998, which claims the benefit under 35 U.S.C. 119(e) of U.S. Application No. 60/080,970, filed April 7, 1998, and U.S. Application 60/067,740, filed December 2, 1997.

Please replace the paragraph beginning on page 10, line 26 of the specification with the following replacement paragraphs.

Figs. 15A-E: A β levels in the cortex of 12-month old PDAPP mice treated with AN1792 or AN1528 in combination with different adjuvants. The A β level for individual mice in each treatment group, and the median, mean, and p values for each treatment group are shown.

Fig. 15A: The values for mice for the PBS-treated control group and the untreated control group.

Fig. 15B: The values for mice in the AN1528/alum and AN1528/MPL-treatment groups.

Fig. 15C: The values for mice in the AN1528/OS21 and AN1792/Freund's adjuvant treatment groups.

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Fig. 15D: The values for mice in the AN1792/Thimerosal and AN1792/alum treatment groups.

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Fig. 15E: The values for mice in the AN1792/MPL and AN1792/QS21 treatment groups.

Please replace the paragraph beginning at page 29, line 25, with the following replacement paragraph:

Such peptides, proteins, or fragments, analogs and other amyloidogenic peptides can be synthesized by solid phase peptide synthesis or recombinant expression, according to standard methods well known in the art, or can be obtained from natural sources. Exemplary fibril compositions, methods of extraction of fibrils, sequences of fibril peptide or protein components are provided by many of the references cited in conjunction with the descriptions of the specific fibril components provided herein. Additionally, other compositions, methods of extracting and determining sequences are known in the art available to persons desiring to make and use such compositions. Automatic peptide synthesizers may be used to make such compositions and are commercially available from numerous manufacturers, such as Applied Biosystems (Perkin Elmer; Foster City, California), and procedures for preparing synthetic peptides are known in the art. Recombinant expression can be in bacteria, such as *E. coli*, yeast, insect cells or mammalian cells; alternatively, proteins can be produced using cell free *in vitro* translation systems known in the art. Procedures for recombinant expression are described by Sambrook et al., *Molecular Cloning: A Laboratory Manual* (C.S.H.P. Press, NY 2d ed., 1989). Certain peptides and proteins are also available commercially; for example, some forms of A β peptide are available from suppliers such as American Peptides Company, Inc., Sunnyvale, California, and California Peptide Research, Inc. Napa, California.

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Please replace the paragraph beginning at page 30, line 21, with the following replacement paragraph:

In a further variation, an immunogenic peptide, such as a fragment of A β , can be presented by a virus or a bacteria as part of an immunogenic composition. A nucleic acid encoding the immunogenic peptide is incorporated into a genome or episome of the virus or bacteria. Optionally, the nucleic acid is incorporated in such a manner that the immunogenic peptide is expressed as a secreted protein or as a fusion protein with an outer surface protein of a virus or a transmembrane protein of a bacteria so that the peptide is displayed. Viruses or bacteria used in such methods should be nonpathogenic or attenuated. Suitable viruses include adenovirus, HSV, Venezuelan equine encephalitis virus and other alpha viruses, vesicular stomatitis virus, and other rhabdo viruses, vaccinia and fowl pox. Suitable bacteria include SalmonellaSalmonella and ShigellaShigella. Fusion of an immunogenic peptide to HBsAg of HBV is particularly suitable. Therapeutic agents also include peptides and other compounds that do not necessarily have a significant amino acid sequence similarity with A β but nevertheless serve as mimetics of A β and induce a similar immune response. For example, any peptides and proteins forming β -pleated sheets can be screened for suitability. Anti-idiotypic antibodies against monoclonal antibodies to A β or other amyloidogenic peptides can also be used. Such anti-Id antibodies mimic the antigen and generate an immune response to it (*see Essential Immunology* (Roit ed., Blackwell Scientific Publications, Palo Alto, 6th ed.), p. 181). Agents other than A β peptides should induce an immunogenic response against one or more of the preferred segments of A β listed above (e.g., 1-10, 1-7, 1-3, and 3-7). Preferably, such agents induce an immunogenic response that is specifically directed to one of these segments without being directed to other segments of A β .

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Please replace the paragraph beginning at page 77, line 6, with the following replacement paragraph:

Preparation of the pBx6 protein: An expression plasmid encoding pBx6, a fusion protein consisting of the 100-amino acid bacteriophage MS-2 polymerase N-terminal leader sequence followed by amino acids 592-695 of APP (β APP) was constructed as described by Oltersdorf et al., J. Biol. Chem. 265, 4492-4497 (1990). The plasmid was transfected into

B⁵ $E. coli$ and the protein was expressed after induction of the promoter. The bacteria were lysed in 8M urea and pBx6 was partially purified by preparative SDS PAGE. Fractions containing pBx6 were identified by Western blot using a rabbit anti-pBx6 polyclonal antibody, pooled, concentrated using an Amicon Centriprep tube and dialysed against PBS. The purity of the preparation, estimated by Coomassie Blue stained SDS PAGE, was approximately 5 to 10%.

Please delete the following phrase on page 88, line 7:

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Please replace the paragraph beginning at page 91, line 17, with the following replacement paragraph:

B_b To prepare formulation doses with alum (Groups 1 and 5). A β peptide in PBS was added to Alhydrogel (two percent aqueous aluminum hydroxide gel, Sargeant, Inc., Clifton, NJ) to reach concentrations of 100 μ g A β peptide per \pm 2 mg of alum. 10X PBS was added to a final dose volume of 200 ml in 1X PBS. The suspension was then gently mixed for approximately 4 hr at RT prior to injection.

Please replace the paragraph beginning at page 92, line 3, with the following replacement paragraph:

To prepare formulation doses with Freund's Adjuvant (Group 4), 100 µg of AN1792 in 200 µl PBS was emulsified 1:1 (vol:vol) with Complete Freund's Adjuvant (CFA) in a final volume of 400 µl for the first immunization. For subsequent immunizations, the antigen was similarly emulsified with Incomplete Freund's Adjuvant (IFA). For the formulations containing the adjuvants alum, MPL or QS21, 100 µg per dose of AN1792 or AN1528 was combined with alum (\pm 2 mg per dose) or MPL (50 µg per dose) or QS21 (25 µg per dose) in a final volume of 200 µl PBS and delivered by subcutaneous inoculation on the back between the shoulder blades. For the group receiving FA, 100 µg of AN1792 was emulsified 1:1 (vol:vol) with Complete Freund's adjuvant (CFA) in a final volume of 400 µl and delivered intraperitoneally for the first immunization, followed by a boost of the same amount of immunogen in Incomplete Freund's adjuvant (IFA) for the subsequent five doses. For the group receiving AN1792 without adjuvant, 10 µg AN1792 was combined with 5 µg thimerosal in a final volume of 50 µl PBS and delivered subcutaneously. The ninth, control group received only 200 µl PBS delivered subcutaneously. Immunizations were given on a biweekly schedule for the first three doses, then on a monthly schedule thereafter on days 0, 16, 28, 56, 85 and 112. Animals were bled six to seven days following each immunization starting after the second dose for the measurement of antibody titers. Animals were euthanized approximately one week after the final dose. Outcomes were measured by ELISA assay of A β and APP levels in brain and by immunohistochemical evaluation of the presence of amyloid plaques in brain sections. In addition, A β -specific antibody titers, and A β -dependent proliferative and cytokine responses were determined.

Please replace the paragraph beginning at page 92, line 25, with the following replacement paragraph:

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Table 1011 shows that the highest antibody titers to A β 1-42 were elicited with FA and AN1792, titers which peaked following the fourth immunization (peak GMT: 75,386) and then declined by 59% after the final, sixth immunization. The peak mean titer elicited by MPL with AN1792 was 62% lower than that generated with FA (peak GMT: 28,867) and was also reached early in the immunization scheme, after 3 doses, followed by a decline to 28% of the peak value after the sixth immunization. The peak mean titer generated with QS-21 combined with AN1792 (GMT: 1,511) was about 5-fold lower than obtained with MPL. In addition, the kinetics of the response were slower, since an additional immunization was required to reach the peak response. Titers generated by alum-bound AN1792 were marginally greater than those obtained with QS-21 and the response kinetics were more rapid. For AN1792 delivered in PBS with thimerosal the frequency and size of titers were barely greater than that for PBS alone. The peak titers generated with MPL and AN1528 (peak GMT 3099) were about 9-fold lower than those with AN1792. Alum-bound AN1528 was very poorly immunogenic with low titers generated in only some of the animals. No antibody responses were observed in the control animals immunized with PBS alone.

Please replace the paragraph beginning at page 94, line 1, with the following replacement paragraph:

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The results of AN1792 or AN1592 treatment with various adjuvants, or thimerosal on cortical amyloid burden in 12-month old mice determined by ELISA are shown in Figs. 15A-15E. In PBS control PDAPP mice (Fig. 15A), the median level of total A β in the cortex at 12 months was 1,817 ng/g. Notably reduced levels of A β were observed in mice treated with AN1792 plus CFA/IFA (Fig 15C), AN1792 plus alum (Fig 15D), AN1792 plus MPL (Fig 15E) and QS21 plus AN1792 (Fig 15E). The reduction reached statistical significance ($p<0.05$) only for AN1792 plus CFA/IFA (Fig 15C). However, as shown in Examples I and III,

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the effects of immunization in reducing A β levels become substantially greater in 15 month and 18 month old mice. Thus, it is expected that at least the AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 compositions will achieve statistical significance in treatment of older mice. By contrast, the AN1792 plus the preservative thimerosal (Fig 15D) showed a median level of A β about the same as that in the PBS treated mice. Similar results were obtained when cortical levels of A β 42 were compared. The median level of A β 42 in PBS controls was 1624 ng/g. Notably reduced median levels of 403, 1149, 620 and 714 were observed in the mice treated with AN1792 plus CFA/IFA, AN1792 plus alum, AN1792 plus MPL and AN1792 plus QS21 respectively, with the reduction achieving statistical significance ($p=0.05$) for the AN1792 CFA/IFA treatment group. The median level in the AN1792 thimerosal treated mice was 1619 ng/g A β 42.

Please add page 96 after page 95.

Please delete the following paragraph on page 98, line 12:

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Please delete the following paragraph on page 100, line 11:

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